IMPAACT Network Overview

1.0 INTRODUCTION AND MISSION

The International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) group is a new Leadership Group representing a merger of investigators from the Pediatric AIDS Clinical Trials Group (PACTG) and the Perinatal Scientific Working Group of the HIV Prevention Trials Network (HPTN/HIVNET). The group will be headed by group Chair, **Brooks Jackson**, MD, MBA (Johns Hopkins). Social & Scientific Systems, Inc. (SSS), will support the Coordinating and Operations Center (CORE). The Statistical Data Management Center (SDMC) for the IMPAACT group will be SDAC/FSTRF headed by **Terry Fenton**, Ed.D (Harvard). **Susan Fiscus**, PhD (U North Carolina), will head the Central Laboratory Network structure for the group. The mission of the IMPAACT group, which is worldwide in scope, will be to significantly decrease the mortality and morbidity associated with HIV disease in pregnant women, children, and adolescents by:

1) Developing and evaluating safe and cost effective approaches for the interruption of mother-to-infant transmission
2) Evaluating treatments for HIV-infected children, adolescents, and pregnant women, including treatment and prevention of co-infections and co-morbidities
3) Evaluating vaccines for the prevention of HIV sexual transmission among adolescents

The PACTG and HPTN investigators have designed and performed the clinical trials that have yielded data to set the standards of care for children infected with HIV and for the interruption of vertical transmission throughout the world (see Appendix B for PACTG and HPTN network publications highlights). In addition, they have elucidated the pathogenesis of HIV MTCT and infection in infants and children both in the United States and in international settings. These studies have included chemoprophylactic trials and a number of Phase I/II HIV vaccine trials for infected infants, children, and pregnant women. The PACTG has been a joint effort of the National Institute of Allergy and Infectious Diseases (NIAID) and the National Institute for Child Health and Human Development (NICHD) since 1993, with a total of 42 research units in the United States and 10 units in Brazil, Thailand, and South Africa. The HPTN perinatal group (formerly HIVNET), funded by a consortium of NIH institutes, has been conducting prevention-of-mother-to-child transmission (PMTCT) studies internationally since 1994, with a total of nine clinical trial units in Uganda, Tanzania, Malawi, Zambia, Zimbabwe, South Africa, Brazil, and India. The IMPAACT group has proposed to work with CTUs shown in Table 1.

Table 1. Proposed number and locations of CTUs for IMPAACT network

	#	IMPAACT CTU Sites
United States	16-18	Boston, Chicago, Houston, Los Angeles, Memphis, Newark, New Orleans, Philadelphia, San Diego, Worcester + 6-8 additional sites
Africa	11	Botswana, Ethiopia, Malawi, South Africa, Tanzania , Uganda, Zambia, Zimbabwe
South America	1	Brazil
Asia	3	Thailand

The patient population served by IMPAACT will be broad-based and mostly composed of impoverished pregnant women, infants, children, and adolescents of diverse racial

and ethnic backgrounds. Without a strong network devoted to these patient groups, studies would be severely limited and often nonexistent. While multiple research entities are focused on research in adults, IMPAACT is unique in its mission of research in HIV-infected pregnant women and children. A major strength of the IMPAACT network is that now both HIV prevention and treatment interventions will be accessible to women, children, and adolescents in the IMPAACT networks at domestic and international sites. IMPAACT is also composed of the most experienced and productive domestic and international investigators in the world for conducting HIV prevention/treatment trials in these populations. The most prominent U.S. and international clinical scientists have been selected to form IMPAACT's leadership. They have strong relationships with other AIDS Clinical Trials Networks (U.S. and European), with pharmaceutical companies, and with the MTCT-Plus and PEPFAR programs. These clinical scientists are committed to the formation and maintenance of a productive network focused on efficiently answering questions of global relevance. The new IMPAACT leadership has already designed a streamlined protocol development and implementation process. Ideas for new protocols will be considered from individuals within and outside the Network, and critically and rapidly evaluated by the IMPAACT network. The IMPAACT leadership will liaison with experienced site investigators, whose long-term involvement will depend on ongoing protocol enrollment to a high standard. Importantly, IMPAACT leadership will work closely with DAIDS, NICHD, and NIMH utilizing their expertise to enhance and ensure that IMPAACT pushes forward with creative solutions to relevant problems, and with the highest scientific integrity.

IMPAACT has an ambitious scientific agenda that proposes to carry forward 28 PACTG, four HPTN, and one ATN treatment and prevention trials (transition protocols) and develop 26 new protocols. In the first year, we estimate that IMPAACT will enroll approximately 9,434 women, children, and adolescents in developing countries into 23 protocols (eight new and 15 transition protocols) and 1,479 subjects in the United States into 19 protocols (four new and 15 transition protocols) (see Tables 2 and 3). These protocols will be in four of the six RFA-designated high-priority areas (PMTCT, translational research/drug development, optimization of clinical management including co-morbidities, and vaccines).

Table 2. Number of IMPAACT protocols (number of protocols that will enroll in Year 1)

	MTCT	Translational	Optimization	Vaccine[1]	All
International					
New	4 (1)	5 (3)	8 (3)	4 (1)	21 (8)
Transition	9 (9)	2 (2)	4 (4)	0 (0)	15 (15)
All International	13 (10)	7 (5)	12 (7)	4 (1)	36 (23)
U.S. Only					
New	0 (0)	3 (3)	2 (1)	0 (0)	5 (4)
Transition	5 (4)	9 (7)	4 (4)	0 (0)	18 (15)
All U.S.	5 (4)	12 (10)	6 (5)	0 (0)	23 (19)
All New	4 (1)	8 (6)	10 (4)	4 (1)	26 (12)
All Transition	14 (13)	11 (9)	8 (8)	0 (0)	33 (30)
All Studies	18 (14)	19 (15)	18 (12)	4 (1)	59 (42)

[1]Includes only HIV vaccine studies that will enroll HIV-uninfected youth. Other vaccine studies are included under MTCT, Translational, or Optimization (as in IMPAACT Overview section).

Table 3. Projected total accrual* in Years 1-7 (projected accrual in year 1)

	MTCT[1]	Translational	Optimization	Vaccine[2]	All
International					
New	7100 (20)	418 (75)	4180 (125)	2110 (300)	13808 (520)
Transition	17115 (7809)	40 (40)	1610 (1065)	0 (0)	18765 (8914)
All Int'l	24215 (7829)	458 (115)	5790 (1190)	2110 (300)	32573 (9434)
US Only					
New	0 (0)	154 (129)	400 (30)	0 (0)	554 (159)
Transition	1620 (737)	367 (332)	419 (251)	0 (0)	2406 (1320)
All US	1620 (737)	521 (461)	819 (281)	0 (0)	2960 (1479)
All New	7100 (20)	572 (204)	4580 (155)	2110 (300)	14362 (679)
All Transition	18735 (8546)	407 (372)	2029 (1316)	0 (0)	13371 (10234)
All Studies	25835 (8566)	979 (576)	6609 (1471)	2110 (300)	35533 (10913)

*For studies with a range of projected accrual (other than P1031A), the maximum was used.
[1]Mother-infant pairs are counted as 1 enrollment. The total for MTCT international transition studies includes approximately 6,800 women (3,470 in year 1) expected to be enrolled in P1031A, have negative HIV test results, and not to be followed further. Also includes all pairs enrolled to NICHD-HPTN 040/P1043 (IMPAACT and non-IMPAACT sites).
[2]Includes only HIV vaccine studies that will enroll HIV-uninfected youth. Other vaccine studies are included under MTCT, Translational, or Optimization (as in IMPAACT Overview section).

The IMPAACT leadership acknowledges that the number of projected protocols and subject enrollment in year one projects an idealized performance scenario. However, even with delays the number of active protocols and subjects enrolled will still be significantly higher than the number last year in the HPTN and PACTG due to a shift to more international protocols, a more streamlined protocol development and approval process, a greater incentive for domestic sites to enroll in interventional trials, and use of less restrictive inclusion/exclusion criteria.

1.1 SUCCESSES, CHALLENGES, AND SCIENTIFIC PRIORITIES

1.1.1 SUCCESSES. The IMPAACT investigators of this leadership group have had enormous success in preventing mother-to-infant transmission and decreasing mortality among HIV-infected children in the United States (Table 4). The landmark PACTG 076 trial and subsequent trials with highly active antiretroviral therapy (HAART) regimens started earlier in pregnancy and cesarean section have reduced vertical transmission rates from 25% to less than 2% in nonbreastfeeding populations [2;3]. Internationally, IMPAACT investigators have conducted several landmark trials (HIVNET 012, PETRA, SAINT, PHPT2, NVAZ) that have demonstrated that simple, inexpensive antiretroviral regimens can safely reduce mother-to child transmission (MTCT) by 40-50% in breastfeeding populations in the most impoverished countries in the world [4-10]. Likewise, development and implementation of new treatment strategies for HIV-infected children and adolescents have dramatically reduced mortality in high- and mid-resource countries. The PACTG has conducted more than 55 primary therapy protocols for treatment of HIV infection, 28 protocols for the treatment of the complications of HIV infection and drug toxicities, and 28 perinatal protocols. These studies have contributed to the licensure of more than 10 drugs for use in HIV-infected children and HIV-infected pregnant mothers in the United States. Data from the observational, long-term followup

PACTG 219 study document that HIV infection of children has shifted from a rapidly and invariably fatal disease to a chronic illness with mortality below 1% per year [11].

Table 4. Selected landmark clinical trials conducted by IMPAACT investigators

Sponsor	Number or name	Type	Location	Brief Description	Outcome
PACTG	076	Perinatal	US	ZDV vs. placebo to prevent transmission	2/3 reduction with ZDV
HIVNET	012	Perinatal	INTL	SD NVP vs. ultra-short ZDV to prevent tx.	1/2 reduction with NVP
BI	SAINT	Perinatal	INTL	NVP vs ZDV+3TC to prevent perinatal tx.	NVP equivalent to ZDV+3TC
WHO	PETRA	Perinatal	INTL	ZDV+3TC vs placebo to prevent perinatal tx	1/2 reduction with ZDV+3TC
NICHD	PHPT 2	Perinatal	INTL	ante/intrapartum ZDV vs ZDV+NVP	2% tx with ZDV+NVP
NIH DDCF	NVAZ	Perinatal	INTL	postpartum ZDV +NVP vs NVP	36% reduction with ZDV/NVP
HPTN	024	Perinatal	INTL	Antibiotics for chorioamnionitis to prevent tx	Not effective
PACTG	043	ARV	US	ZDV Ph II	ZDV licensed for children
PACTG	152	ARV	US	Ph III ZDV vs. ddI vs. ZDV/ddI for therapy	Combination effective
PACTG	338	ARV	US	Ph II/III ZDV+3TC vs ZDV+3TC+RTV vs D4T+RTV	RTV licensed for children
PACTG	382	ARV	US	Ph II/III EFV	EFV licensed for children
PACTG	326	Vaccine	US	Ph I/II Canarypox HIV vaccine in newborns	Vaccine immunogenic
PACTG	1008	OI	US	Safety of d/c of TMX/SMZ after HAART	Safe

PACTG investigators have also tested several HIV vaccines (ALVAC, Vaxgen, Chiron) in newborns of HIV-infected mothers showing that lymphoproliferative (LPA), cytotoxic lymphocyte (CTL), and humoral immune responses can be elicited and are comparable to that seen in vaccinated adults [12-16]. A number of vaccine trials have also been conducted showing that HIV infected infants and children can successfully mount an immune response to Pneumococcus (PACTG 1024), Varicella zoster (PACTG 292), and influenza (PACTG 1057). IMPAACT investigators have also led the way in the development and evaluation of assays for the diagnosis of HIV infection in infants [17-19], monitoring of viral load [20-25], drug resistance assays [26-30], antiretroviral pharmacology assays [31-41], and cellular and humoral immunology assays [42-46]. The SDMC for the IMPAACT group will be SDAC (with data management provide by FSTRF), which has a distinguished record of achievement in providing support for statistical analysis, data management, and innovative trial designs for the PACTG and the Adult ACTG (AACTG) since 1987. The excellent collaboration between SDAC and the SSS Operations Center since 1986 will continue and should be viewed as a major strength of the new IMPAACT network. The investigators of these two networks have set the standard of care domestically and internationally for the prevention of MTCT and treatment of children and adolescents through the design and implementation of successful multicenter protocols. In addition, the IMPAACT network will provide added value to the studies of other networks such as the ATN, ACTG, and HVTN in collaboration on adolescent vaccines, women's health, and treatment trials.

1.1.2 CHALLENGES. Despite the enormous advances in the knowledge of how to treat HIV-infected children and adolescents and how to prevent mother-to-infant transmission of HIV, the World Health Organization (WHO) estimates that in 2004, approximately 2.2 million children are currently HIV infected worldwide. Approximately 640,000 infants were newly infected in 2004, or 1,800 children per day, and 490,000 HIV-infected

children died in 2004. In sub-Saharan Africa, the location of two-thirds of the HIV epidemic, an estimated 23.4 million adults and 2.0 million children are HIV infected. WHO estimates that less than 10% of the 3 million HIV-infected pregnant women receive any form of antiretroviral therapy for prevention of MTCT and that of 3.8 million adults and adolescents who qualify for treatment according to WHO guidelines, less than 4% are receiving any form of antiretroviral therapy. Because the mortality rate of HIV-infected infants is 40% at 18 months of age in Africa [5] and 90% by 3 years of age [47], most of the perinatally infected children in Africa qualify for treatment, but less than 2% receive antiretroviral therapy due to the expense, lack of pediatric formulations, and/or societies' priority of treating working adults. PMTCT is complicated by the fact that most mothers in Africa breastfeed for 1-2 years after birth due to the risks and expense of formula feeding, the stigma of not breastfeeding, societal pressures, and convenience. Consequently, approximately one-third of MTCT of HIV occurs through breastfeeding. The simple, affordable antiretroviral regimens, such as single-dose nevirapine to mother and infant perinatally, only prevent intrapartum and very early breastfeeding transmission so that neither antepartum nor breastfeeding transmission is prevented. These routes account for 50-60% of MTCT transmission in breastfeeding populations. In addition, in Africa, even where voluntary counseling and testing (VCT) and ARV prophylaxis is offered for prevention of MTCT, uptake is relatively poor, with 20-40% of pregnant women in high-HIV seroprevalence sites refusing HIV testing and up to half of women with known HIV infection not taking ARV prophylaxis as determined by cord blood ARV drug levels [48]. Complicating this situation is the fact that exposure to even a single dose of nevirapine or 3TC can result in detectable genotypic drug resistance mutations, which may compromise future treatment options [26;34;49-51]. Clearly, our current approaches do not adequately address PMTCT and treatment in many of the most affected communities. Novel practical and cost-effective strategies need to be developed.

In much of the developing world, HIV seroprevalence is high among female and male adolescents with seroprevalence rates of 21% among teenage girls having sex in Southern Africa and three times higher than adolescent males [52]. Outside of sub-Saharan Africa, India, Brazil, and Thailand have had significant numbers of HIV-infected children and adolescents numbering in the tens of thousands. Vaccine interventions for young teenagers and preteens are needed to protect this vulnerable population. Prior to availability of these vaccines safe, affordable, effective treatment and prevention strategies are needed both to decrease and to treat HIV-infected pregnant women, children, and adolescents.

In the United States the epidemic is relatively smaller, but contrary to popular belief, the number of HIV-infected children and adolescents continues to increase. It is estimated that of the 40,000+ new HIV cases in the United States each year, 25% occur in adolescents aged 13 to 19 years, with half of all new infections identified in persons below 24 years of age [53;54]. Of the 2,763 HIV-infected children and adolescents in the PACTG 219 study, 32% have CD4 cell percentage <25% and more than half have viral loads >400c/mL so that HIV complications and drug toxicities are predicted to still prove substantial. Moreover, HIV-infected children are at special risk of toxicities from long-term use of ARVs during the decades of growth and development. Although the perinatal transmission rate has been significantly reduced, NIAID PACTG sites report they care for over 5,000 HIV-infected infants, children, and youth. Therefore, although decreased perinatal transmission has led to a dramatic decline in newly identified HIV-infected infants, the decrease is balanced by increased longevity of HIV-infected children as well

as increased numbers of newly infected youth, especially among minorities. Over 7,000 HIV-infected pregnant women give birth in the United States annually, and this year the NIAID PACTG domestic sites reported following over 80 HIV-infected infants <2 years old.

The populations of HIV-infected pregnant women, children, and adolescents are quite different domestically and in developing countries. For the domestic sites, the majority of perinatally infected children/adolescents are treatment experienced by 1 year of age [55], whereas youth infected as adolescents are relatively healthy and antiretroviral naive. Nearly all identified HIV-infected pregnant women receive antiretroviral treatment to prevent perinatal transmission and do not breastfeed. On the other hand, in most developing countries, antiretroviral treatment for HIV-infected pregnant women and their children is not available or is only available for prevention of perinatal transmission. Only 10,000-14,000 (or 2%) of HIV-infected infants receive antiretroviral treatment, and most have advanced disease [56]. The majority of adolescents who become infected are not aware of their infection as they are relatively healthy and do not seek treatment. In addition, diseases such as tuberculosis (TB), malaria, diarrheal diseases, and pneumonia are major causes of mortality in developing countries even among HIV-uninfected children. Therefore, levels of mortality and morbidity remain high despite success of perinatal interventions. Funding from the Global AIDS Fund and PEPFAR for the eventual treatment of 2-3 million people each is an important foundation, but considering that it is likely most of the 26 million HIV-infected individuals in Africa alone will progress to AIDS over the next 10 years, more affordable, effective, safe, and feasible prevention and treatment strategies are needed.

1.1.3 SCIENTIFIC PRIORITIES. The IMPAACT group is committed to conducting studies that will advance the interruption of mother-to-infant transmission and improve prevention and treatment interventions for children and adolescents internationally as well as within the United States. To achieve these goals, we propose to conduct studies in four of the six RFA-designated high-priority areas (PMTCT, translational research/drug development, optimization of clinical management including co-morbidities, and vaccines). *Vaccine protocols for prevention of breastfeeding transmission are in the perinatal section. Therapeutic vaccines in the translational and optimization sections, and vaccines for prevention of sexual transmission are described in the vaccine section.*

1.1.3.1 PMTCT (52% of network funds) Although perinatal transmission has dropped to less than 2% in the U.S., in developing countries approximately 640,000 MTCT infections occur each year. Shorter ARV regimens have proven to be efficacious [57-59], but overall effectiveness is suboptimal due to later transmission via breastfeeding, the limited efficacy of shorter regimens in the antenatal period, and the difficulty of implementing programs for VCT and PMTCT regimens. In addition, even short regimens of nevirapine or 3TC can rapidly select for drug resistance that may potentially limit future treatment options in HIV+ women and children. The perinatal agenda will evaluate new ARV regimens to prevent MTCT during the perinatal period with special emphasis on low resource areas, evaluate MTCT prevention strategies to minimize development of ARV resistance in mothers and infants, focus on interventions such as use of ARVs and vaccines to prevent breastfeeding transmission, evaluate strategies to increase population-based coverage of MTCT prevention, and assess ARV PK and toxicities in pregnant women. Substudies to evaluate the role of HIV subtype, host genetics, drug

resistance, pharmacodynamics, HIV-specific immunity, and HIV viral load in compartments in PMTCT are also planned.

Specific Aim 1: To develop and improve simple, safe, and effective ARV regimens to prevent mother-to-child HIV transmission in the perinatal period with special emphasis on low-resource areas.

1. A Phase III efficacy trial of **Tenofovir vs Nevirapine** in HIV+ women presenting late in pregnancy. *INTL N=2500 pairs;* In Development Open 10/2006
2. A Phase III efficacy trial of **ZDV+ Tenofovir vs ZDV + Nevirapine** in HIV+ women presenting earlier in pregnancy. *INTL N=2500 pairs;* (awaiting results of PACTG 394 and HPTN 057) Open 7/2006
3. A Phase III randomized trial to evaluate safety and efficacy of NNRTI sparing regimens **(trizivir vs combivir+kaletra**) for treatment of pregnant women naïve to and not needing treatment (**PACTG 1039)**. *US N=440 pairs;* Open
4. A Phase III efficacy trial to evaluate 3 different postpartum ARV regimens (ZDV vs ZDV+NVP vs ZDV+3TC+NFV) in infants of non-breastfeeding mothers who did not receive ARVs in pregnancy **(HPTN 040/PACTG 1043).** *Brazil, South Africa N=1731 pairs;* Open

Specific Aim 2: To optimize MTCT-related ARV treatment strategies to improve maternal and infant health through the reduction of ARV resistance and improved safety.

1. A prospective observational study of HIV infected pregnant women is underway that evaluates factors related to disease management, treatment, MTCT, prevalence of genotypic drug resistance, and virological failure **(PACTG 1025)**. *US N=1600;* Open. This study has also allowed the rapid enrollment of women into PACTG 1026 for timely evaluation of PK and safety of new ARVs in pregnancy and assessment of ARV resistance.
2. An observational study to assess safety and toxicity in infants born to women enrolled in ARV treatment trials in developing countries **(PACTG 1054/A5190).** *INTL N=270-410;* Open 9/2005
3. A Phase II study of the pharmacokinetics of nevirapine and the incidence of nevirapine resistance mutations in HIV-infected women receiving single dose **nevirapine alone or in combination with ZDV/ddI or ZDV/ddI/LPV/r (PACTG 1032).** *Thailand N=150;* Open 9/2005
4. A Phase III trial to compare the safety, reduction in viral load, and development and persistence of drug resistance of two PI based ARV regimens **(Kaletra vs Nelfinavir)** in women with recurrent pregnancies **(CS 4057).** *US N=480 pairs;* Open 3/2006

Specific Aim 3. To evaluate simple, safe, and effective interventions to prevent HIV transmission through breastfeeding.

1. A phase III trial to evaluate the safety and efficacy of extended **nevirapine** dosing to infants for 6 months vs placebo to prevent breastfeeding transmission **(HPTN 046).** *Africa N=1576 pairs;* Open 7/2005
2. An observational study to assess whether maternal receipt of HAART during breastfeeding is associated with reduced breastfeeding HIV transmission. **(PACTG 1054/A5190).** *INTL N= 270-410 ;* Open 9/2005

3. A Phase I active vaccine study to evaluate the safety and immunogenicity of **ALVAC 1521 vaccine** in neonates of breastfeeding HIV-infected women. **(HPTN 027).** *Uganda N=50*; Open 10/2005
4. Phase I trial of MVA/Fowlpox vaccine in HIV-exposed newborns *US N=50* Early development; Open 12/2006
5. Phase II trial of MVA/Fowlpox vaccine and passive HIV-specific neutralizing antibody in HIV-exposed neonates. *INTL N=50* Early development; Open 2007
6. A Phase III trial using best neonatal candidate vaccines (active ± passive) will then be tested in breastfed newborns of HIV+ mothers. *INTL N=1600;* Early development Open 2008

Specific Aim 4. To evaluate population-based strategies for prevention of mother-to-child HIV transmission among childbearing populations receiving PMTCT care in limited-resource settings or with limited access to structured antenatal PMTCT programs.

1. A community/clinic intervention in Africa to compare a standard community MTCT program with one in which enhancements are undertaken to increase VCT uptake, use of rapid testing, and community activation to lessen stigma and increase antenatal attendance. Anonymous cord blood testing for HIV status and nevirapine will be used to assess efficacy. *INTL N=5400;* In Development Open 2007
2. A cluster randomized study of counseling and rapid HIV testing of pregnant women with undocumented serostatus who present for delivery in South Africa. The study compares the feasibility, acceptance, performance, and efficacy of intrapartum vs postpartum VCT in South Africa (**PACTG 1031a**). *INTL N= potentially 3300 pairs followed;* Open

Specific Aim 5. To determine the pharmacokinetics, safety, tolerability, and toxicity of ARVs used for PMTCT HIV transmission and maternal health management

1. A prospective Phase I study to evaluate PK of currently prescribed ARVs and interacting combinations in pregnant HIV infected women for which there are little data available (**PACTG 1026s)**. *US N=200;* Open
2. A Phase I/II trial to evaluate the safety and PK of **tenofovir** in HIV infected pregnant women and their infants **(PACTG 394).** *US N= 20 pairs;* OPEN
3. A Phase I/II trial to evaluate the PK and safety of **tenofovir** in HIV infected pregnant women with additional doses to their infants **(HPTN 057).** *Brazil and Malawi N=98 pairs;* Open 10/2005

1.1.3.2 TRANSLATIONAL RESEARCH/DRUG DEVELOPMENT (12% of network funds) In this priority area we plan to conduct translational research in three areas:

1) Primary antiretroviral therapy for treatment of HIV infection
2) Prevention and treatment of the complications of HIV infection and ARV drug toxicities.
3) Therapeutic HIV vaccines

Specific Aim 1: To evaluate the pharmacokinetics and safety of new ARVs and formulations leading to optimal labeling and licensing for infected infants, children, and adolescents. Of the 20 ARVs licensed for use in HIV-infected adults, only 10 are licensed for use in children and fewer still for young infants. In addition, infant

formulations are only available for ZDV, D4T, 3TC, DDI, ABC, NVP, APV, RTV, NFV, and Kaletra [60]. The PACTG has conducted over 55 primary therapy studies that have evaluated pharmacokinetics of these drugs, however much remains to be learned about newer drugs and combinations to optimize efficacy and minimize toxicity. The following new and continuing phase I/II trials will study the PK and safety of ARVs, new ARV formulations, and alternative dosing strategies.

1. Phase I/II trial of the PK, safety and tolerance of combination **Emtricitabine, Efavirenz, and DDI** in HIV-1 infected, treatment naïve, pediatric subjects (**PACTG 1021)** *US N=53; Open*
2. A Phase I/II study of safety, tolerance, and PK of high dose **Lopinavir/Ritonavir (Kaletra)** with or without **Saquinavir** in HIV-infected pediatric subjects previously treated with protease inhibitors **(PACTG 1038)**. *US N=48;* Open
3. An intensive PK study of ARV combinations (Kaletra+Saquinavir or Kaletra+EFV or LPV+SQV+EFV) which have not been well defined in children **(PACTG 1058)**. *US N=96;* Open 6/2005
4. A Phase I/II comparative PK study of GPOvir chewable tablets and the original **3TC, d4T and NVP** liquid formulations in HIV-Infected Thai children. This study will be the first assessment of a fixed dose combination tablet for children **(PACTG 1056)**. *Thailand INTL N=48*; Open 9/2005
5. Phase I/II open-label study of non-peptidic protease inhibitor TMC-114 in combination with optimized ARV background in multi-PI experienced HIV+ children and adolescents. **TMC-114** has potent in vitro antiviral activity against wild-type and PI-resistant HIV-1. *US N=60;* Early development
6. Phase I/II open label study of the NNRTI BILR 355 in combination with optimized ARV background in multi-PI experienced HIV+ children and adolescents. *US N=60;* Early development

Several pharmaceutical companies have also expressed a commitment to studying new agents in children once safety is demonstrated in adults. These include **Pfizer's new CCR5 inhibitor,** which is in phase I trials in adults [61]; and **Tibotec's new NNRTI (TMC278),** which shows potent antiviral activity and a favorable resistance profile compared with other NNRTIs [62].

Specific Aim 2: To evaluate safety and/or immunogenicity of approaches for the prevention and treatment of co-infections, ARV toxicities and associated metabolic complications, and developmental complications of HIV infection. Co-infections in HIV infected infants, children, adolescents, and pregnant women result in substantial morbidity and mortality especially in resource poor settings. Diarrheal disease, malaria, malnutrition, and pneumonia are significant causes of substantial morbidity and mortality [63]. Among TB Patients in South Africa, the HIV seroprevalence rates among those <18 months old was 52% [64]. In order to reduce morbidity and mortality and delineate drug-drug interactions, IMPAACT will initiate phase I/II trials designed to prevent or treat co-infections including TB, HPV, and rotavirus; ARV toxicities including metabolic; and neuropsychiatric and developmental complications of HIV.

1. Phase I/II study to evaluate the pharmacokinetic profile of **antiretrovirals and anti-tuberculosis medications** when co-administered to HIV/TB infected children. *INTL N= 96;* In Development

2. Phase I/II trial to evaluate safety and immunogenicity of booster doses of **BCG vaccine** given at 6 months and 12 months to asymptomatic, HIV infected infants on ARV therapy. *INTL N=72;* In Development
3. Phase I/II trial of **Stressgen,** a fusion protein of the Mycobacterium bovis heat shock *protein* 65 and the HPV 16 Ey protein for the treatment of low-grade squamous intraepithelial lesions (**PACTG 1046)**. *US N=40* Open 9/2005
4. Phase II-A, randomized, double-blinded, placebo-controlled trial of **Gardasil™ Quadravalent HPV** types 6, 11,16,18 L1 virus-like particle (VLP) vaccine to prevent HPV infection in HIV-infected children ≥7-<12 years of age **(PACTG 1047).** *US N=142;* Open 10/2005
5. Phase II trial to assess the safety, immunogenicity, and reactivity of three doses of **oral live attenuated rotavirus vaccine** given at time of routine vaccinations in HIV infected infants. *INTL N=150;* In Development
6. **A Phase I/II dose-finding study** to determine pharmacokinetics and safety of **atorvastatin** for treatment of PI-associated increased LDL-cholesterol in HIV-infected children and adolescents. *US N= 80*; In Development
7. Phase II safety and pharmacokinetic study of psychiatric medications (stimulants, antidepressives), when used with ARVs in HIV Infected youth with ADHD or depression. *US N=40;* In Development

Specific Aim 3. Determine safety, immunogenicity, and affect on viral replication of candidate vaccines in infected infants, children, and adolescents. Long-term adherence is challenging for all HIV-infected individuals, especially youth. Even when ARV adherence and viral suppression are achieved, long term treatment is associated with significant drug-related morbidity. Thus, there is a pressing need for alternative strategies that would allow preservation of health with reduced exposure to ARVs. Our hypothesis is that stimulation of HIV immunity (particularly during early infection) with an HIV vaccine during HAART therapy will maximize viral suppression and boost immune function so that viral load setpoint is lowered. Children and youth generate more vigorous immune responses to neoantigens compared to adults presumably due to their greater thymic potential. This holds true for healthy populations as well as individuals with cancer and HIV [65-67]. Therefore, therapeutic immunization probably has the most potential in young HIV infected individuals (ie infants, children, and youth). We plan to perform the following trials:

1. A Phase I trial of safety and tolerability of **recombinant HIV-1 MVA and fowlpox vaccines (Therion)** in HIV infected young adults (age 18-25 yr) with control of HIV replication on stable HAART. **(PACTG 1059)** *US N=16;* Open
2. A Phase I/II trial of the safety and immunogenicity of **Merck Ad5 trivalent vaccine** in HIV infected adolescents and children. *US.N=60; Open* 9/2006
3. A Phase I/II trial of safety and immunogenicity of **HIV-1 MVA and fowlpox vaccine (Therion)** in HIV infected children and adolescents (age 2-18 yr) effectively treated with HAART prior to 3 months of age. **(PACTG 1033)** *US N=16;* Open early 2006
4. A Phase I/II study of HIV-1 MVA and fowlpox vaccines (Therion) in HIV infected infants treated with HAART from <3 mo of age. *US and INTL N= 40*; In Development
5. A Phase I/II study of safety, tolerability and immunogenicity of **DNA dendritic cell vaccine** (**Dermavir)** in HIV infected children and adolescents on HAART. **(PACTG 1049)** *US. and Intl N=32.* Early Development**.**
6. A substudy of PACTG 219c (NWCS 088) will be performed to identify long term non-progressors (LTNP) and determine the role of host genetic/immunologic factors, coreceptor usage, and replicative fitness in LTNP. *US N=100*; In Development

1.1.3.3 OPTIMIZATION OF CLINICAL MANAGEMENT, INCLUDING CO-MORBIDITIES. **(34% of network funds).** IMPAACT has identified the following strategic areas of primary therapy, immune based therapies, and treatment of co-infections/toxicities, where carefully constructed clinical studies can yield data that will improve the outcomes of HIV-infected infants, children and adolescents worldwide.

Specific Aim 1. Evaluate ARV treatment strategies in infants, children, adolescents that have the potential to result in greater and more prolonged suppression of viral load, enhanced immune response, decrease mortality, toxicity, and drug resistance, produce more affordable regimens, and less expensive assay monitoring. The ARV treatment strategy trials listed below of early vs deferred treatment, treatment interruption, ARV class sparing treatments, ARV switching strategies, and treatment regimens to maximize adherence will be conducted domestically and in developing countries where ARV expense and long-term toxicities are major issues, especially in growing children and adolescents.

When to Start – A number of infants and children mount an effective immune response to HIV and do not qualify for treatment under WHO guidelines. Two studies are proposed to evaluate whether early vs deferred treatment makes a significant difference in disease outcome:
1. A Phase II randomized study to assess the safety and efficacy of early versus delayed HAART treatment in HIV-infected Infants <7 months of age on disease outcome of 1-5 Years of age in Brazil (**PACTG 1048**) *INTL N= 220;* in late development stage; Open 9/2005
2. A Phase III strategy trial to evaluate the relative benefit of immediate versus delayed initiation of ARV therapy among previously untreated children **(PACTG 1035).** *INTL N=300;* Open 1/2006

Treatment Interruption Strategies – A proportion of HIV infected children who stop ARV treatment indicate that some children do not virologically or immunologically progress [68-70]. Studies examining various strategies to maximize immune function, while minimizing ARV toxicities and expense, are needed. Within these studies parameters that predict success with intermittent ART and need for continuous ART will be identified.
1. A two-armed randomized trial comparing targeted treatment discontinuation with standard of care in HIV-infected adolescents. *US N=200;* In Development; Open late 2006

Strategies to deal with ARV Resistance – Three trials will compare specific multi-drug regimens or cycling of different HAART regimens for suppression of HIV replication. In addition, protocols will examine the efficacy of NNRTI-ART regimens in nevirapine exposed vs unexposed infants
1. A randomized clinical trial comparing the responses to initiation of NNRTI-based versus PI-based antiretroviral therapy in HIV-infected infants who have and have not previously received single dose Nevirapine for PMTCT in South Africa. (**PACTG 1060)**. *INTL N=480*; Open Fall 2005
2. A Phase II, randomized, open-label study of safety and effectiveness of two antiretroviral therapeutic strategies: a dual PI-based HAART vs a multi-NNRTI based ART regimen in ART-experienced children and youth who have experienced virologic failure (**PACTG 1053)**. *US N= 254;* Open 7/2005

3. A randomized, open-label pilot study of cycling combination antiretroviral therapy regimens and a standard HAART regimen in highly antiretroviral experienced subjects <24 years of age (**PACTG 1044).** *US N= 30;* In Development; Open Fall 2005

Second-Line Therapy for Children Failing NNRTI-based first line treatment is a priority area within Africa and Asia, as to which second-line regimen is most efficacious and least toxic.
1. A Phase III trial is planned to compare two different second-line regimens for efficacy and long/short-term toxicity using **ZDV+ddI** with **ATZ vs. Kaletra**. *INTL N=480;* In Development

Toxicity/Adherence
1. A Phase III randomized comparative trial of protease-containing and protease sparing HAART regimens in HIV-infected adolescents with evaluation of therapeutic drug monitoring (PACTG 1034). *US N=240* Open
2. A Phase II/III randomized comparative study to compare the safety and toxicity using two standard generic ARV regimens in Africa, **D4T + 3TC + NNRTI vs ZDV + 3TC + NNRTI** in infants and children who meet WHO guidelines for antiretroviral treatment in sub-Saharan Africa, includes the potential to add third arm of **ZDV + 3TC + tenofovir** if formulation and dosing available. *INTL N=200;* In Development, Open mid-2006
3. A Phase II/III randomized comparative study of toxicity, adherence, and efficacy of once daily **EVF + FTC + TDF** compared with twice daily fixed dose combination of **NVP+3TC+D4T** in ARV naïve children in Africa, Brazil, and Thailand. *INTL N=300*; In Development, Open 2008

Specific Aim 2: To conduct studies leading to the optimal use of vaccines, prophylactic regimens and therapies for prevention and treatment of co-infections in HIV infected and exposed infants, children, adolescents, and pregnant women.
Communicable diseases represent seven out of the top 10 causes of child deaths, account for 60% of all child deaths, and are substantially higher among HIV-infected children [63]. Malnutrition and multiple concurrent illnesses (i.e., pneumonia and diarrheal illnesses) contribute to these high death rates. In HIV-infected children, rates of these diseases increase as does morbidity and mortality. HIV-infected pregnant women also have higher rates of morbidity and mortality, compared to HIV-uninfected pregnant women, primarily due to preventable diseases including influenza, malaria, and pneumonia [71]. Our goal is to conduct studies leading to the rapid development and optimal labeling and licensing of new vaccines, prophylactic regimens, and therapies for prevention of opportunistic infections in HIV-infected and exposed infants, children, adolescents, and pregnant women.

1. Phase III, randomized, open-label trial of three hepatitis B vaccination schemas in HIV-infected youth **(ATN 024).** *US N=369;* Open
2. Phase III randomized placebo-controlled trial of an **HPV vaccine** in HIV-infected youth *US/INTL N=1000.*
3. Phase III randomized placebo-controlled efficacy trial of rotavirus vaccine in HIV infected and exposed infants *INTL N=600*; Open early 2008
4. Phase II, randomized study of safety and immunogenicity of **influenza vaccine** compared with tetanus vaccine in HIV-infected pregnant women in developing countries. *INTL N=600*; In Development
5. A Phase III, randomized, double blind, placebo controlled trial to determine the efficacy of Isoniazid (INH) in preventing tuberculosis disease and latent tuberculosis

infection among South African infants with perinatal exposure to HIV **(PACTG 1041).** *INTL N=1300;* Open
6. A Phase III, randomized, placebo controlled trial of continuing **cotrimoxozole prophylaxis** in HIV infected infants at 12 months of age with CD4>15%. *INTL N=500;* In Development, Open 9/2006
7. A Phase II, randomized, open label trial comparing two **malaria prophylaxis** regimens in HIV-infected pregnant women living in high-risk areas for malaria in Africa. *INTL N=500;* In Development

Specific Aim 3: To conduct studies to evaluate, prevent, and treat the complications of pediatric HIV infection and antiretroviral drugs, including but not limited to metabolic disorders, neurologic and psychiatric co-morbidity, and other complications.

1. A randomized trial of stimulants compared with selective norepinephrine reuptake inhibitors for treatment of HIV+ adolescents with ADHD. *US N=200;* In Development
2. A Data Analysis Concept Sheet will assess causes of morbidity and mortality of HIV infection and ARV therapy among HIV+ children enrolled in international IMPAACT trials with >2 years of follow-up.

1.1.3.4 VACCINES FOR PREVENTION OF SEXUAL HIV TRANSMISSION (2% of network funds). Newborn infants of HIV-infected breastfeeding mothers, preadolescents, and adolescents will be the primary target populations of any successful preventive HIV vaccine. NIAID has conducted over 60 clinical HIV vaccine trials to date, yet, except for PACTG 218, very few youth under 18 years have been included in trials despite their high risk of infection. In order to license a vaccine for use in this group, safety, immunogenicity, and efficacy data in this population are needed. In parts of sub-Saharan Africa, the annual HIV seroincidence rates in 15- to 19-year-old teenage girls are as high as 18.9% [72]. Many women less than 20 years of age access prenatal care at HPTN sites with excellent follow-up rates of retention. We believe that uninfected young women will be ideal to test the efficacy of an HIV-preventive vaccine, once safety and immunogenicity have been demonstrated in adults. However, the relevant hurdles, such as ethical, legal, regulatory, and feasibility issues, need to be addressed so that this at-risk population can be included in future prevention trials.

Specific Aim 1. To evaluate and implement an effective vaccine regimen to prevent sexual transmission of HIV-1 in adolescent and pre-adolescent populations.
(NOTE: Vaccine specific aims with respect to therapeutic vaccines and vaccines for the prevention of breastfeeding transmission are under Translational Research and PMTCT sections, respectively.)

We will build on the existing infrastructure of the antenatal clinics used in IMPAACT perinatal trials to 1) confirm HIV seroprevalence and incidence rates among teenage girls attending antenatal clinics and their adolescent sisters, 2) educate and involve the community regarding vaccine trials, and 3) perform Phase I/II safety and immunogenicity trials in this population before proceeding to an efficacy trial. A number of efforts are currently underway within the PACTG (US and international) and the ATN (US) to prepare sites for enrollment in future trials. Three PACTG sites in South Africa will complete pilot studies to identify potential adolescent subjects and to involve

communities. We aim to collaborate with the ATN and HVTN to evaluate vaccines in pre-teen and adolescent populations.

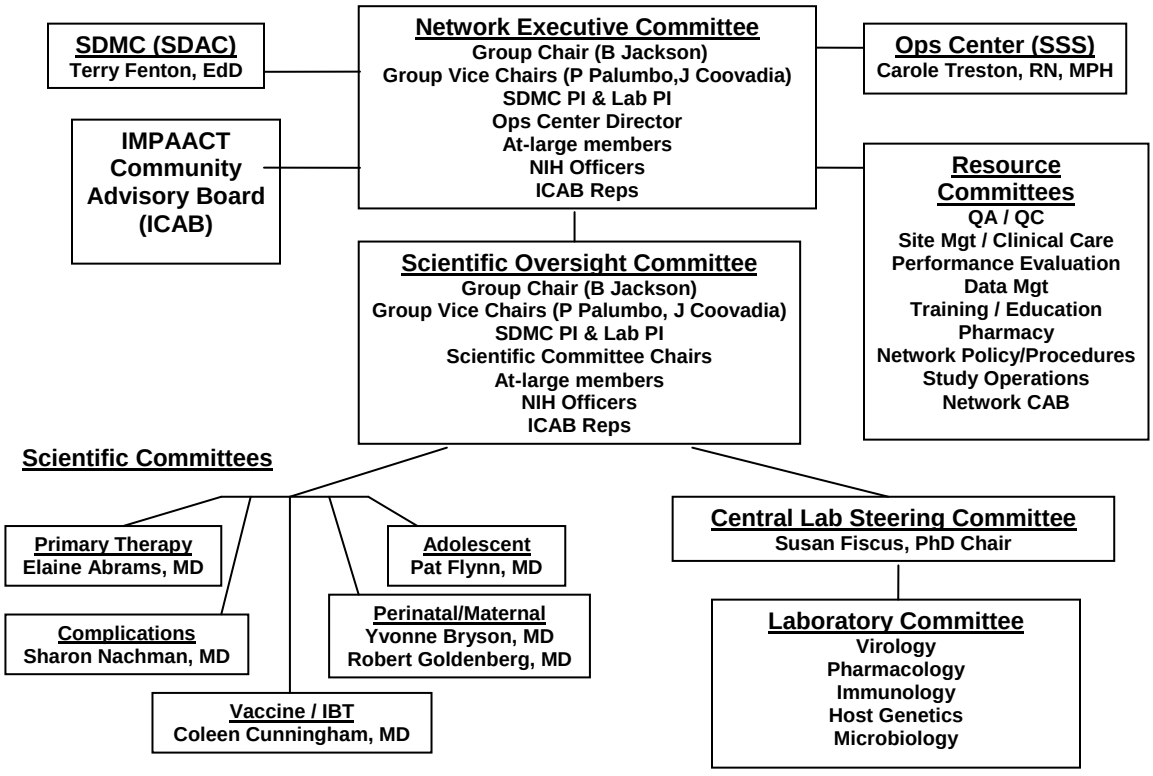
The most promising vaccine candidates include HIV-1 vaccines with Ad5 vectors (Merck) [73;74] and the VRC DNA vaccine [75]. Other possible candidates include MVA constructs, NYVAC, and adeno-associated virus. We will work with the governmental agencies and vaccine manufacturers to access promising candidate vaccines as early as possible in the developmental process. In collaboration with the ATN and the HVTN we plan to proceed first with evaluations of the Merck Ad5 and Therion MVA/fowlpox products for safety and immunogenicity in HIV infected and uninfected youth domestically and internationally. We will continue to consider newer products as they become available. Collaboration with the HVTN for co-endorsement of protocols and to standardize assays and reagents will be critical for interpretation across studies. Our plan is to identify the appropriate adolescent populations and prepare the community to ultimately conduct a Phase IIb or Phase III preventive vaccine efficacy trial in adolescents after safety and immunogenicity have been demonstrated in adults. The following studies are planned:

1. **Prospective evaluation of HIV seroincidence, sexual behaviors, and factors influencing vaccine trial participation** in select cohort of at risk youth (13-20 yr of age) with high HIV seroprevalence rates. *Africa. US&INTL N=1000;* Early Development Open 9/2006
2. **Phase I trial** of safety and immunogenicity of HIV **MVA/Fowlpox vaccine** (Therion) in HIV infected young adults **(PACTG 1059)** *US. N= 16;* Open
3. **Phase I/II dose finding trial** of safety and tolerability of HIV **Merck Ad5 vaccine** in HIV infected adolescents and children. *US and other clade B sites N=50;* Early Development
4. **Phase I trial** of safety and immunogenicity of HIV **Merck Ad5 vaccine** in HIV negative adolescents. *US and other clade B sites N=60;* Early Development
5. **Phase I trial** of safety and immunogenicity of HIV **MVA/Fowlpox vaccine** (Therion) in HIV negative youth (13-18 yo) *US&INTL. N= 50;* Early Development
6. **Bridging study** of most promising candidate vaccine in HIV negative, at risk youth populations. *US/ Intl N=1000;* Plan for late 2007

1.1.4 TRANSITION OF CLINICAL RESEARCH ACTIVITIES. Of the protocols listed above that will be carried forward into the IMPAACT group, 28 PACTG protocols and four HPTN protocols (027, 040, 046, and 057), and one ATN protocol (024) are likely to be ongoing at the time of the award. An additional 26 PACTG protocols will be largely completed with residual followup (nine protocols) or in analysis (17 protocols). PACTG protocols will be supported by SDAC, SSS, and the IMPAACT Central Lab. The HPTN 027, 046, and 057 protocols will continue to be supported by SCHARP, FHI, and the HPTN Central Lab until completion. HPTN 040 will be supported by WESTAT (funded by NICHD) and partially by the HPTN Central Lab for lab QA/QC. Table 1 in section 2.2 describes all the protocols by scientific section, and Figure 1 in section 2.2 shows the timeline of protocols transitioning to the IMPAACT group.

1.2 ORGANIZATIONAL STRUCTURE. *To accomplish its mission and goals, the IMPAACT Leadership Group will comprise the following three components: the CORE, the SDMC, and the Central Laboratory Network. An overview of the IMPAACT organization is shown in the Figure 1-1, below.*

Figure 1-1.IMPAACT Leadership Organizational Structure



1.2.1 COORDINATING AND RESEARCH OPERATIONS CENTER (CORE). The CORE comprises the Group Chair; the Operations Center; the Network Executive Committee (NEC); and its scientific and resource committees.

1.2.1.1 NETWORK EXECUTIVE COMMITTEE (NEC). Under the direction of the Group Chair, the NEC will set the scope of the scientific agenda, be responsible for the finances, administration, evaluation, and policies of the network, budget signoff of protocols and substudies, and interactions across networks and with DAIDS and other NIH institutes. Reporting to the NEC will be the Scientific Oversight Committee (SOC), the CORE Operations Center (Social & Scientific Systems), SDMC, ICAB, and nine Resource committees.

1.2.1.2 THE SCIENTIFIC OVERSIGHT COMMITTEE (SOC), also under the direction of the Group Chair, will determine the scientific agenda and scientific priorities, review and approve concepts for protocol development, and give scientific signoff of protocols and substudies. The SOC can direct Scientific Committees to develop specific protocols. Reporting to the SOC will be the following:

- **Five Scientific Committees** will conceive and develop protocols, implement research strategies, monitor protocol development and implementation, and will be accountable for the use of resources within their committees. Each scientific committee will have up to 12 voting members. Voting members will consist of experts from each of the following geographic areas: South America, Asia, Sub-Saharan Africa, and United States. The committees and their chairs are as follows:

– **Vaccine/Immune Based Therapy Committee** chair - Coleen Cunningham, MD
– **Primary Therapy Committee** chair - Elaine Abrams, MD
– **Complications of HIV Committee** chair - Sharon Nachman, MD
– **Perinatal Committee** co-chairs - Yvonne Bryson, MD, (Peds); Robert Goldenberg, MD, (OB)
– **Adolescent Committee** chair - Patricia Flynn, MD

- **Laboratory Steering Committee.** This committee, chaired by Susan Fiscus, PhD, reports to the SOC in order to coordinate the scientific priorities of the laboratories and scientific committees and is responsible for the QA/QC of the central Network and site laboratories. The Committee's responsibilities will include: coordination of laboratory scientific priorities, assessment of laboratory issues for open and closed protocols for which laboratory testing is still ongoing, biannual review of laboratory performance, mechanisms for restricting protocol testing based on poor proficiency testing performance, and review of discretionary fund requests.

- **Protocol Evaluation Committee.** This committee will ensure that the protocol is consistent and feasible from a site perspective in conducting the protocol. Reviews of final protocols will take place after Scientific Committee signoff prior to formal review by the SOC to ensure that the protocol procedures are internally consistent and any ambiguities are clarified.

- **Study Monitoring Committee**. This committee, chaired by Terry Fenton, PhD will review each network study at least every 6 months by assessing enrollment, retention, quality of data reporting, adherence to regimen and study visits compared with targets, and any safety issues that may arise. A progress report and recommendations will be made to the NEC, SOC, Scientific Committee, and protocol team. In the case where the conduct of a protocol needs improvement or revisions, recommendations will be made to include specific corrective action plans that need to be taken to achieve a given level of performance within a specific time frame. These recommendations may include closure of a protocol. This committee will be extremely important for the ongoing critical review of protocol performance in order to achieve excellent scientific results and efficient use of network resources.

- **Publications Committee.** This committee chaired by Paul Palumbo, MD, reviews and approves network manuscripts and abstracts prior to submission, monitors writing timelines, tracks IMPAACT Network publications, and ensures that the network is in compliance with NIH publication/media policies.

1.2.1.3 NEC RESOURCE COMMITTEES

1. Quality Assurance /Quality Control (QA/QC) Committee, Audrey Kamrin (UCSF) – Chair; Merleesa Naidoo (Johannesburg, South Africa) – Vice-Chair. The QA/QC Committee will be responsible for assuring processes to improve the quality of the data at the site level, including protocol adherence, source documentation, and regulatory adherence.

2. Site Management and Clinical Care Committee. Carol Vincent (U Penn) – Chair. This committee will oversee and resolve operational and clinical care issues identified by affiliated clinical research sites.

3. Performance Evaluation Committee. Diane Wara, MD (UCSF) – Chair. This committee will develop and implement standard criteria and processes for assessing progress of each structural component of the network, including sites, operations office, laboratories, data management center, scientific and resource committees, and protocol teams.

4. Data Management Committee. Gary Koutsoubis (U Penn) – Chair. Jane Lindsey MSc, ScD (Harvard) – Vice Chair. This committee will oversee and resolve network issues pertaining to case report forms (CRFs) and data entry.

5. Training and Education Committee - Maripat Toye (Baystate MA) – Chair; Mary Jo Hoyt (UMDNJ) –Vice-Chair. This committee will assess training needs within the network, implement training activities that can be accessed by any site, evaluate effectiveness of training, and collaborate with Training and Education Committees of other funded networks.

6. Pharmacy Committee. **Vivian Rexroad**, PharmD (Johns Hopkins) – Chair; Diana Clark (Harvard) – Vice-Chair. This committee will work with representatives of the DAIDS Pharmaceutical Affairs Branch to identify protocol and site specific training needs and provide a forum for communication and information exchange among network pharmacists.

7. Network Community Advisory Board Committee. Domestic Co-Chair – Dorothy Shaw (UAB), International Co-Chair – Wandoa Mwambu (Tanzania). This committee will participate in development and implementation of a community involvement plan domestically and internationally to facilitate community participation in network and cross-network activities and represent roles and requirements of local site CABs. Activities will include: 1) building community capacity goals for conducting specific research; 2) building awareness and education to improve the community's understanding of research; 3) building community mobilization skills; 4) finding ways to assess the community's research priorities; and 5) developing mechanisms for sites to share best practices, experiences, and lessons learned.

8. Network Policy and Procedures Committee, Wendy Levy – Chair (SSS). This committee will be responsible for developing a Manual of Policies and Procedures for the network. This manual will be updated at least annually by the committee and reviewed and approved by the NEC for distribution to all network sites and leadership members.

9. Study Operations Committee. Elizabeth Hawkins – Chair (SSS) This committee will monitor the implementation of IMPAACT studies, focus on operational issues and challenges encountered at specific sites or by specific studies, and refer issues and make recommendations on policy to protocol teams, NEC, DAIDS and other Network groups for further discussion, direction and resolution.

1.2.1.4 CENTRAL OPERATIONS CENTER. SSS will serve as the administrative/ management agent for the IMPAACT CORE under the direction of the group chair and the NEC. Responsibilities include the following:

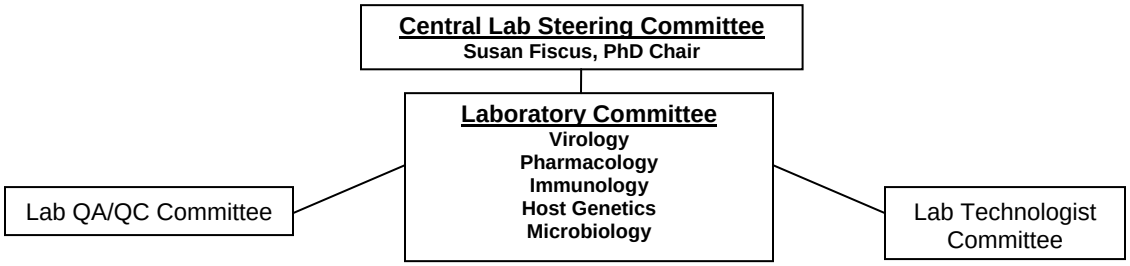
- Administers the central grant, provides overall financial management, and is the contracting agent for the CORE and for funds provided by pharmaceutical companies in support of IMPAACT research
- Supports the development and review of all IMPAACT scientific protocols and remains involved through protocol implementation and study closure

- Provides a central point of coordination, communications, and support to the IMPAACT network executive leadership and to virtually all committees, protocol teams, and working groups of the IMPAACT group
- Arranges all network meetings and provides on-site support during the meeting

1.2.2 CENTRAL LABORATORY NETWORK. The Central Laboratory is a network of laboratories and their investigators with special expertise in virology, immunology, pharmacology, bacteriology, mycology, parasitology, host genetics, and general laboratory QA/QC control issues. There will also be a laboratory subcommittee for QA/QC issues and a laboratory technologist committee to provide technical assistance to site laboratories and protocol teams (see Figure 1-2). The laboratory network will be led by Susan Fiscus, PhD, who will serve as the Chair of the Laboratory Steering Committee and will serve as a voting member on the NEC and SOC. She will also be the IMPAACT network's representative for lab-related issues with the other network lab PIs.

Figure 1-2.

Central Lab Network



An essential part of therapeutic and prevention trials is identification and evaluation of new tests, reagents, and instruments for clinical studies that integrate treatment with measures of adherence, outcome, and pathogenesis. The assays to be evaluated and implemented include assessments of viral replication, techniques to evaluate HIV genotype and phenotype and host genotype, improved approaches to monitoring drug levels including new drugs, novel techniques to assess HIV pathogen specific immune responses, and detection and quantitation of non-HIV pathogens. These will be standardized across networks where possible.

Domestically, there will be four specialty labs with complementary expertise in HIV virology, four labs with complementary expertise in immunology, four labs with complementary expertise in pharmacology, a microbiology lab with specific expertise in bacteriology, mycology, and parasitology, and one lab with expertise in host genetics (i.e., HLA, pharmacogenetics, and chemokine receptor genetics), which will also manage a DNA repository. The Central Laboratory network will make arrangements with investigators who have special expertise and/or assays for protocols requiring specialized testing not provided by the central network laboratories. Assays that lend themselves to centralized testing such as viral load testing, CD4 cell counts, and standard lipid assays will be subcontracted to a CLIA approved clinical lab with excellent turnaround time on a fee-for-service basis.

Internationally, site laboratories will perform as much protocol testing as possible such as heme/chemistry tests, CD4 counts, viral load, pregnancy testing, microbiology (ie blood cultures, malaria smears, TB testing) and HIV antibody testing. However, regional

labs will be established and supported with cross network collaboration in Africa, South America, and Asia for specialized testing (i.e., genotypic resistance testing, vaccine related immunology assays, pharmacology ARV assays, special flow cytometry assays).

The laboratory investigators of the Central Lab network will also be active participants in protocol design and generation of pathogenesis based substudies. Training and assistance with QA for site laboratories, specialized domestic laboratories, and international regional laboratories will be provided initially by an inter-network laboratory QA committee, but will transfer to a Contract Resource Organization funded by DAIDS.

1.2.3 STATISTICAL AND DATA MANAGEMENT CENTER (SDMC). The SDMC comprises the Statistical and Data Analysis Center (SDAC) and the Data Management Center (DMC). The SDAC is led by Terry Fenton, Ed.D, and is headquartered at the Harvard School of Public Health. Senior-level biostatisticians provide complete statistical support, from study design through data analysis and publication. These biostatisticians are among the leading experts in clinical trial design and analysis; are core members of each protocol team; prepare and present interim analyses to an independent Data and Safety Monitoring Board; conduct the primary analysis described in the protocol, as well as secondary analyses; and interact with other networks to standardize cross protocol analyses and evaluation criteria. Data management at the DMC is provided by Frontier Science Technology and Research Foundation (FSTRF) of Amherst, New York. Mr. Greg Pavlov is the executive director of this group of experienced clinical data managers who use advanced system technologies to collect data from remote sites to a central mainframe computer.

1.2.4 IMPAACT NETWORK SITES. In order to carry out the proposed scientific agenda, we anticipate that the network will require 16-18 NIAID-funded domestic clinical trial units (CTU) to enroll approximately 1479 subjects in year one into 19 different domestic protocols and 15 international clinical trial units (11 in Africa, 1 in South America, and 3 in Thailand) to enroll approximately 9434 subjects in year one into 23 different international protocols. In addition, NICHD clinical sites will also participate in IMPAACT trials, which have typically contributed 30-35% of subjects for PACTG trials. The aforementioned clinical trial units will comprise the IMPAACT site network. The proposed IMPAACT CTUs were selected after formal review by IMPAACT group leadership and external reviewers based on the sites' available populations, HIV seroprevalence and incidence, infrastructure, drug access, clinical trials experience, data quality, investigators' track records, community support, and accrual/retention experience.

1.3 NETWORK KEY PERSONNEL. Key personnel for the IMPAACT network have been elected by the investigators of the existing PACTG and HPTN networks. It is anticipated that several additional key personnel will be added to the NEC, SOC, and Central Laboratory network once the CTUs have been awarded. Key personnel of the IMPAACT leadership are not only accomplished, senior investigators in the field of perinatal/ pediatric/ adolescent HIV prevention and treatment, but also have extensive experience in conducting domestic and international HIV prevention and treatment clinical trials and pathogenesis based substudies. Key personnel and committee members will include African, South American, and Asian investigators in order to provide the broad experience and expertise required for the relevant international trials.

CORE Group Chair and PI Brooks Jackson, MD, MBA, Professor of Pathology (Johns Hopkins University), has had experience with HIV clinical trials groups since 1987, when

he first joined the combined Adult/Pediatric ACTG. He has held leadership positions in both the PACTG and AACTG, being the chair of the Joint Virology Committee, chair of the Virology Technical Advisory Committee, a member of the AACTG Scientific Agenda Steering Committee, the HIV Disease RAC committee, and PI of Virology labs for the PACTG and AACTG. He has also held leadership positions in the HIVNET and HPTN groups as the co-chair of the HIVNET Scientific Steering Committee, chair of the HIVNET perinatal scientific committee, and a member of the HPTN's Executive Committee, Prevention Leadership Group, Protocol Review Committee, Network Evaluation Committee, and Study Monitoring Committee. He has been the PI of the HPTN Central Laboratory, PI of the HIVNET Uganda site, and PI of the HPTN China sites. His experience as protocol chair includes the HIVNET 006 and 012 trials, an extended nevirapine/ HIV immuneglobulin trial in Uganda for PMTCT, a study of targeted vs universal nevirapine trial for PMTCT in Uganda, and a Phase I/II trial of nevirapine pre-prophylaxis in high-risk HIV-negative adults in Baltimore.

International Group Vice-Chair Hoosen Coovadia, MD, Professor of Pediatrics (University of Natal, Durban, South Africa), is the Victor Daitz Chair and Director of the Centre for HIV/AIDS Networking and the Scientific Director of the Doris Duke Medical Research Institute at U of Natal, Durban, South Africa. He has nearly 30 years of experience in the care of children in South Africa and has conducted numerous HIV PMTCT trials, including the PETRA and SAINT trials. He has published over 200 papers in the field and is internationally recognized for his work in pediatric/maternal HIV care and prevention studies. Dr. Coovadia will focus his efforts on ensuring relevant trials and infrastructure are developed for resource-poor countries.

Domestic Group Vice-Chair Paul Palumbo, MD, Professor of Pediatrics (University of Medicine and Dentistry New Jersey), has extensive domestic experience in pediatric AIDS clinical trials. He has served in a number of leadership roles in the PACTG as group vice-chair since 2000, past chair of the Primary Therapy Committee, past chair of the Virology Committee, and a member of Therapeutics Leadership Group of the NICHD-funded Adolescent Trials Network. Dr. Palumbo will focus his efforts on ensuring relevant trials are developed for the Unites States and other developed countries.

SDMC PI Terry Fenton, EdD, Principal Research Scientist (Harvard School of Public Health), is the PI of the current SDMC for the PACTG. He has been a member of the PACTG Executive Committee throughout the group's history and has been integrally involved with developing its scientific agenda and overseeing statistical support. This has included taking the lead statistical role in over 30 ongoing or developing clinical trials, including three perinatal studies involving pregnant HIV-infected women and their infants; 11 primary therapy trials of new antiretroviral therapies; seven vaccine trials involving immunotherapy, prophylaxis, or prevention of mother-to-child transmission; seven studies of non-vaccine immune-based therapies; and five trials involving complications of HIV disease.

Central Lab Network PI Susan Fiscus, PhD, Professor of Microbiology & Immunology and Pathology & Laboratory Medicine (University of North Carolina), has been Director of the University's Retrovirology Core Laboratory, an AACTG Virology Laboratory since 1989, a PACTG Virology Laboratory since 1993, and Virology Core Director for UNC's CFAR since 1998. She has experience with many existing networks domestically and internationally. The focus of her research has been PMTCT, including breastmilk transmission, and developing assays for HIV quantification in genital secretions, CSF, saliva, and breastmilk.

Virology Specialty Lab PIs –	**S Fiscus** (UNC), **S Eshleman** (JHU), **G Aldrovandi** (USC), **L Frenkel** (U Wash)
Immunology Lab PIs –	**S Douglas** (UPENN), **K Luzuriaga** (U MASS), **S Pahwa** (U Miami), **S Spector** (UCSD)
Pharmacology Lab PIs –	**E Caparelli** (UCSD), **C Fletcher** (U Colorado), **E Acosta** (UAB), **F Aweeka** (UCSF)
Host Genetics Lab PI –	**S Spector** (UCSD)
Microbiology Lab PI –	**K Carroll** (JHU)

Scientific Committee Chairs

Vaccines/IBT Committee Chair Coleen Cunningham, MD, Assoc Professor of Pediatrics, (Duke University), is now the Chair of the PACTG Vaccine/IBT Research agenda committee. She has also been a member of the PACTG Executive Committee, Protocol Evaluation Subcommittee, chair or vice chair of multiple protocols including PACTG 316, team member of several protocols, and PACTG representative to the HIV Vaccine Trials Network (HVTN). She has also been a member of the Adolescent Trials Network Therapeutics Leadership group and chair of one protocol and vice chair and/or team member for several other studies. She also participates in the adolescent working group and the phase III subcommittee of the HVTN.

Primary Therapy Committee Chair Elaine Abrams, MD, Assoc Professor Pediatrics (Columbia University), has a long history within the PACTG as PI of her unit at Harlem Hospital. She has been on multiple protocol teams and participated in many protocols at her site. Her committee work has included primary therapy, the PACTG Executive Committee, and the Protocol Evaluation subcommittee. She is also the Director of the MTCT-Plus Initiative, a foundation-funded HIV care and treatment program for women and children in low- resource, high-prevalence settings. More than 6,500 individuals have been enrolled during the past 18 months in 13 countries in sub-Saharan Africa and Thailand. Dr. Abrams has developed the pediatric and perinatal programming for the Initiative and understands the scientific and implementation issues around ART treatment in low resource settings.

Complications Committee Chair Sharon Nachman, MD, Professor of Pediatrics (SUNY, Stonybrook), has served in a number of leadership positions in the PACTG, including current chair of the Complications of HIV RAC for the PACTG. She has served as chair or vice chair for over 10 PACTG studies, including PACTG 1041 and 1055, focusing efforts on developing protocols in complications of HIV and primary therapy. She has served on numerous committees, including chairing the Appendix 40 committee, which developed the codes used for diagnosis reporting for the PACTG.

Perinatal Scientific Committee Co-Chair Yvonne Bryson, MD, Professor of Pediatrics (UCLA), has served in a number of PACTG leadership positions, including the pediatric executive committee, the perinatal /maternal committee, and the virology group. With other colleagues, she proposed and conducted the first phase I PK and safety study of zidovudine in pregnancy (PACTG 082), which was the basis for the PACTG 076 design. She was chair of the PACTG Perinatal committee when it developed the nevirapine studies (PACTG 250 and 316), the HIVIG PACTG 185 trial to evaluate the role of neutralizing antibody in prevention of MTCT, and the first studies of protease inhibitors in

pregnant women and children. She has been the PI of the UCLA PACTG site and the HPTN Brazil site, where she implemented five clinical trials at four different sites and eight hospitals in Brazil. **Co-Chair Robert Goldenberg, MD**, Professor of Ob-Gyn (U of Alabama), has extensive experience with multi-center research networks. Along with Dr. Taha Taha, he is the protocol co-chair for the phase III HPTN 024 study involving use of antibiotics to reduce chorioamnionitis and perinatal transmission in 3570 mother-infant-pairs, which was completed this past year in Malawi and Zambia.

Adolescent Committee Chair Pat Flynn, MD, Professor of Pediatrics, St Jude Children's Research Hospital (University of Tennessee), has been the chair of the PACTG Adolescent Research Committee. She is PI of the St Jude Hospital PACTG site and has chaired a number of PACTG protocols, including the current Phase I/II PK study (PACTG 394) of tenofovir for PMTCT. Within the ATN, she is chair of ATN 024 that focuses on hepatitis B immunization strategies in HIV-infected youth and co-PI of ATN 025, looking at a vaccine preparedness effort using hepatitis B vaccine in HIV-uninfected youth.

Operations Center Director Carole Treston, RN, MPH (SSS), has been the Operations Center Director for the PACTG since 2002. She has served as the primary representative to NIH in planning and management of technical, administrative and financial functions of the network. She has been responsible for allocation and management of resources for development and implementation of NIH-sponsored clinical research studies, including significant expansion to international sites and activities in low-resource settings. She currently oversees the development and management of annual network budgets in excess of $13 million, an Operations Center budget in excess of $2.5 million, and she ensures that expenditures are executed within NIH and Federal guidelines. She provides strategic and technical input to IMPAACT leadership for planning, implementation, and evaluation of network efforts.

1.4 COORDINATION OF NETWORK COMPONENTS. Coordination of network and inter-network components is important for achieving successful development and implementation of the scientific agenda. Ensuring that this coordination occurs will be dependent on the design of a functional infrastructure and vigilant oversight by CORE, SDMC, Central Lab, Scientific Committees, Resource Committees, and Operations Center.

1.4.1 INTRA-NETWORK COORDINATION. Intra-network coordination starts with coordination of development of the scientific agenda. In the IMPAACT network, the responsibility for setting the scope of the scientific agenda and budget required resides in the Network Executive Committee (NEC), whereas developing, prioritizing, and accountability for the scientific agenda resides in the SOC and its Scientific Committees. For example, the NEC has decided that the scope of the scientific agenda for the IMPAACT group will be limited to the worldwide prevention and treatment of HIV and its complications to infants, children, adolescents, and pregnant women through the breastfeeding period. The SOC has developed and prioritized the scientific agenda within the scope defined. Since the chair, vice-chairs, SDMC PI, Central Lab PI, CCG, NIH, and Operations Center Director of the IMPAACT group lead both the NEC and SOC, a consistent line of authority is maintained and laboratory, statistical, and Operations Center activities are coordinated. At the same time, the SOC activities are dedicated to the scientific agenda issues, and NEC activities are dedicated to administrative, operational, and financial issues critical to the functioning of the network and inter-network activities.

Concept and protocol development will take place within the Scientific Committees and can be either investigator initiated or SOC directed. The five Scientific Committees proposed (Vaccine/IBT, Primary Therapy, Complications of HIV, Perinatal, and Adolescents) for the network were selected because these are areas in which fields of expertise have naturally evolved and it allows efficient protocols development. Scientific Committee chairs will be members on the SOC in order to better coordinate the scientific agenda among Scientific Committee chairs and provide critical expertise to the SOC. Before a concept plan and full protocol are developed, a 1-2 page capsule of a proposed protocol must first be submitted by a Scientific Committee to the SOC for scientific review and approval. If a capsule is approved, a 10-page concept plan is developed in the Scientific Committee, approved by the Scientific Committee chair, and then sent to the SOC and DAIDS CSRC for review and approval (and NEC for budget approval) before developing the full protocol. Once the full protocol is developed, it is sent to the SOC and CSRC for final approval. This process from submission of capsule to SOC to approval of the full protocol by the SOC and CSRC should not take longer than 34 weeks.

We recognize that there will be protocols that have areas of overlap between Scientific Committees, in which case the SOC will direct that specific individuals from each committee work together to develop a protocol that meets certain criteria within a given timeframe and will require the signoff of only one Scientific Committee chair. Like the NEC and SOC, Scientific Committee membership will include representatives from laboratory, SDMC, Operations Center, CCG, NIH and NICHD medical officers, NEC Resource, and international and domestic investigators and staff so that protocols have input and coordinated support for rapid development and implementation. International and domestic protocols in a given area, such as Complications of HIV infection, will be developed within the same Scientific Committee to take advantage of the expertise of both domestic and international investigators and to coordinate protocols that overlap geographic areas or transition from domestic to international settings. In this process, the SOC has the final signoff for the network on the scientific design of a protocol before it proceeds to DAIDS, and NEC has final signoff responsibility from a financial perspective. Since leadership for SOC and NEC are the same, financial and scientific reviews for the network will be efficient and highly coordinated. The time commitments for the group chair, vice-chairs, SDMC, and Central Lab PI will be substantial ($\geq$50% effort) but necessary for this model to be successful as designed. Reviews by different committees are minimized, yet sufficient expertise, continuity, and coordination are maintained throughout the process. **Progress of protocols** once implemented will be reviewed by the respective Scientific Committees every month. The Study Monitoring Committee will also review protocol progress quarterly, to ensure adequacy of enrollment, retention, adherence to study visits, and quality of data reporting. Any safety issues that may arise will be discussed by both the Scientific Committees and the Study Monitoring Committee on an as needed basis.

Administration of the network. The NEC, working through the Operations Center, will be responsible for the operations, administrative requirements, regulatory requirements, finances, and interactions with the Managing Partners and DAIDS. Responsibilities include facilitating cross network collaborations; coordinating protocol development and implementation; coordinating SOP development; tracking progress in study implementation; providing administrative support for the PI, scientific committees, network CAB, and network meetings; maintaining network records and archives; completing and providing reports to DAIDS (annual reports, publication of data,

demographic diversity reports); providing scientific, protocol-specific, and other training as required; and providing fiscal management and oversight of network resources. The Group PI will work closely with DAIDS, the IMPAACT Operations Center Director, and the members of the NEC to ensure that the cost of protocols and operations are realistic and within budget. Assuming a set of fixed costs for the group infrastructure (CORE, SDMC, Central Lab) and for the sites, the cost of implementing protocols will be determined using a formula to calculate the sum of study specific costs of conducting the study at each site. Protocol implementation costs typically include the additional costs for laboratory tests, counselors, nurses, drugs, pharmacists, data entry staff, specific protocol training workshops, and study specific equipment and supplies not covered under site core costs. Study-specific costs may also be incurred for additional SDMC staff or Central Lab test expenses for large protocols.

The **Laboratory Steering Committee (LSC),** like the Scientific Committees, reports to the SOC to coordinate the scientific priorities of the laboratories and scientific committees. The LSC will be chaired by the Central Lab PI (Susan Fiscus, PhD) and membership will include Scientific Committee chairs, Core Laboratory PIs, representatives from the international laboratories, and at large representative from the Scientific Oversight Committee and Network Executive Committee, as well as ad hoc representation from SSS, FSTRF, SDAC, NICHD, and DAIDS. The Committee's responsibilities will include: coordination of laboratory scientific priorities, assessment of laboratory issues for open and closed protocols for which laboratory testing is still ongoing, biannual review of laboratory performance, mechanisms for restricting protocol testing based on poor proficiency testing performance, and review of discretionary fund requests. The LSC will ensure that laboratory research conducted by funded network laboratory investigators is consistent with the scientific agenda and is protocol related or at least is a necessary element in the critical pathway for the development of a specific protocol. The LSC will also make recommendations to the SOC and NEC for discretionary funding for specific laboratory projects, as the Central Laboratory funds will be under the control of the NEC. Reporting to the LSC will be the Laboratory Committee of funded network laboratory investigators, with its Laboratory Technologist subcommittee and Laboratory QA/QC subcommittee. The Laboratory Technologist subcommittee will standardize laboratory procedures (shipping, specimen labeling, storage, cell freezing) across the network and in conjunction with other networks and actively participate in protocol development and review. The Laboratory QA/QC subcommittee will assist, train, and assess network laboratory staff in Good Laboratory Practices and safety and laboratory procedures.

Communications. Coordinating these activities will require not just a well designed organizational structure, but also effective communications between the components of the IMPAACT network and across the networks both domestically and internationally. Therefore, we will have regular committee calls, cross network committee calls, regular calls between IMPAACT Group leadership and DAIDS/NICHD, face-to-face protocol team meetings, and IMPAACT network and cross network operational and scientific meetings. Participation of committee and protocol team members on calls and at meetings will be expected and tracked. The IMPAACT Operations Center will support this communication by setting up conference calls, arranging meetings, maintaining a website of network protocols, members, policies, procedures, meeting information, and a quarterly newsletter. The use of less expensive yet effective communication technology, such as internet voice-over technology, will be adopted, and eventually video-conferencing may be initiated.

1.4.2 CROSS-NETWORK COLLABORATIONS. The IMPAACT group plans to collaborate with the following networks on specific scientific protocols and on coordinating and standardizing areas such as number of site laboratories, laboratory QA/QC, specimen tracking and storage, Community Advisory Boards, SDMC data management, CRF forms, performance evaluations (sites, CORE, SDMC, Central Lab, Network leadership, and DAIDS), training (GCP, fiscal admin, laboratory, pharmacy, clinical care), adverse event reporting, career development, and joint meetings. **Adolescent Trials Network (ATN)—**A number of treatment protocols have been developed jointly, co-sponsored by both networks, and implemented at PACTG and ATN sites. The ATN and IMPAACT leadership groups have agreed to continue this productive collaboration specifically in the areas of domestic adolescent treatment and vaccine protocols. **Pediatric HIV/AIDS Cohort Study (PHACS)—**The PACTG has had a long term observational study (PACTG 219) of approximately 4,300 HIV infected and uninfected children being followed at 88 PACTG NIAID- and NICHD-funded sites. The IMPAACT group will work to transition these subjects into PHACS studies, but is not planning to continue to enroll in the 219 study after March 2006, but would prefer to collaborate in the areas of performing scientific substudies and analyses using the PACTG 219 specimen repository, existing database, and possibly co-enrolling in protocols with the PHACS participants. **Adult AIDS Clinical Trials Group (AACTG)—** IMPAACT investigators through the PACTG have had nearly 20 years of collaboration with the AACTG investigators in a number of scientific and administrative areas and have used the same Operations Center and SDMC, shared many of the same domestic sites, standardized and evaluated a number of laboratory assays together, and held joint network meetings. The IMPAACT group would continue these activities and relationships and collaborate scientifically, specifically in the area of women's health. Operationally, a joint committee has been formed between the AACTG and IMPAACT called the Women's Health and Perinatal Research Collaboration Group consisting of several investigators from each network with interest and expertise in HIV-related women's health issues, particularly in the areas of HIV-related complication and treatment protocols for HIV infected pregnant women. **HIV Vaccine Trials Network (HVTN)—**The IMPAACT group is planning to conduct preventive and therapeutic trials in infants, children, and adolescents domestically and internationally. The HVTN plans its high priority trials in adults domestically and internationally and in high risk adolescent girls in South Africa. These two networks have agreed to collaborate by using the HVTN vaccine laboratory for some immunogenicity assays and standardizing key assays between the groups so that there is comparability of data. We also propose a three-way collaborative group in the area of prophylactic HIV vaccine for adolescents that will include HVTN, ATN, and IMPAACT investigators. That group will function to maintain communication and coordination between the three networks. **HIV Prevention Trials Group (HPTN)—**Although the HPTN perinatal investigators will be joining the IMPAACT group, the HPTN has valuable behavioral expertise that the IMPAACT group plans to take advantage of by accessing the expertise of the HPTN Behavioral Core committee in the areas of drug adherence and VCT uptake**. NICHD Domestic and International Pediatric and Perinatal HIV Clinical Trials Network** – IMPAACT will work closely with the NICHD leadership and investigators, many of whom are in leadership positions within IMPAACT. NICHD sites will continue to have the opportunity to participate in protocol development, IMPAACT leadership positions, and protocol enrollment of subjects at their sites into IMPAACT protocols much as they have with the PACTG.

1.5 UNIQUE FEATURES OF THE IMPAACT NETWORK

1. The IMPAACT network is unique in its mission of research to prevent and treat HIV among infants, children, and pregnant women domestically and internationally. These populations are not likely to be adequately represented in studies proposed by any other leadership group application.

2. The leadership comprises many of the most experienced domestic and international investigators in the world for conducting HIV prevention/treatment trials in these populations. There is substantial depth and breadth of expertise in design, implementation, and analysis of clinical trials; infrastructure development; and evaluation of HIV pathogenesis through lab investigation within clinical trial substudies.

3. IMPAACT investigators have strong relationships with pharmaceutical companies and MTCT-Plus and PEPFAR programs, critical for drug access and development of new drug formulations for infants and children. A major strength of the IMPAACT networks is that both HIV prevention and treatment interventions will be accessible to women, children, and adolescents at domestic and international sites in the IMPAACT network.

4. This network has designed a streamlined protocol development and implementation process. Given the enormous fixed cost of maintaining site capacity and Group Leadership structure, it is essential that relevant protocols are developed and implemented in a timely and coordinated manner.

5. The unique needs and challenges of community representation for pediatric and PMTCT trials is recognized by the IMPAACT network. The demands of parenting a sick child, combined with the parent's illness in an environment of poverty and social problems compete with the opportunity for CAB activism. Consequently, the IMPAACT leadership includes community members; women with HIV infected children from the US and Africa committed to developing and supporting network wide community activities to enhance individual community member's expertise; better incorporate the unique needs of community members at international sites and build CAB capacity both domestically and internationally. The IMPAACT CAB structure will be built on local CABs, whose members will be elected to regional CABs, from which the network CAB members will be elected. Training, mentoring, and support are built into each level of the IMPAACT CAB structure.

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